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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 03/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,905	RONAI, ZE'EV	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,8-13,15-32,35-43 and 45-47* is/are pending in the application.

4a) Of the above claim(s) *16-19,22,30-32 and 45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,8-13,15,20,21,23-29 and 35-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 9, 2005, has been entered.

1. The amendment filed December 9, 2005, is acknowledged and has been entered. Claims 3, 6, 7, 14, 33, 34, and 44 have been canceled. Claims 1, 4, 12, 13, 29, and 35 have been amended. Claims 45-47 have been added.

2. Claims 1, 4, 8-13, 15-32, 35-43, and 45-47 are pending in the application. Claims 16-19, 22, 30-32, and 45-47 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43 are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

5. Newly submitted claims 45-47 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Newly submitted claims 45-47 are directed to a method for inhibiting metastasis of a tumor cell. In contrast, claims 1, 4, 8-12, and 35-43 are drawn to a method for inhibiting the growth of tumor cells; claims 23-29 are directed to a method for treating a

tumor, and claims 13, 15, 20, 21 are directed to a product, namely a polypeptide or a composition thereof.

Although the prior Office action states a treatment that inhibits the growth of tumor cells necessarily also inhibits the metastasis of those cells[1], the now claimed process for inhibiting metastasis of a tumor cell, as recited in newly added claims 45-47, does not necessarily achieve the claimed effect by inhibiting the growth of that tumor cell, as in accordance with the process of claims 1, 4, 8-12, and 35-43.

Stedman's Online Medical Dictionary, 27th Edition, which is available on the Internet at http://www.stedmans.com, defines the term "metastasis" as "[t]he spread of a disease process from one part of the body to another, as in the appearance of neoplasms in parts of the body remote from the site of the primary tumor; [which] results from dissemination of tumor cells by the lymphatics or blood vessels or by direct extension through serous cavities or subarachnoid or other spaces" (Copyright © 2006 Lippincott Williams & Wilkins). In contrast, defines the term "growth" as "[t]he increase in size of a living being or any of its parts occurring in the process of development" (Copyright © 2006 Lippincott Williams & Wilkins).

Accordingly, the invention of claims 45-47 is patentably distinct from the inventions of claims 1, 4, 8-12, and 35-43 because the inventions have different purposes or objectives. The purpose of the inventions of claims 45-47 is to inhibit spread from one part of the body to another of a primary tumor by the metastatic process that involves dissemination of tumor cells. The purpose or objective of the invention of claims 1, 4, 8-12, and 35-43 is to inhibit an increase in size of a tumor. Furthermore, while not necessarily unrelated, the processes of tumor growth and metastasis are nonetheless distinct processes, which are independently regulated. Therefore, the inventions of claims 45-47 and the inventions of claims 1, 4, 8-12, and 35-43 are expected to have different criteria for success, as the polypeptide administered to a patient diagnosed with a tumor may be more or less effective to inhibit the growth of the tumor, as compared to its ability to inhibit its metastasis, and vice

[1] See, e.g., page 16, paragraphs 1 and 2 (section 14) of the prior Office action mailed September 9, 2005.

versa. In addition, because the inventions of claims 45-47 and the inventions of claims 1, 4, 8-12, and 35-43 affect different biological processes (i.e., growth and metastasis), the practice of the inventions necessarily involves the measurement of different endpoints and for this reason, the practice of the different inventions necessarily involves the establishment of different correlations as an indication of the effectiveness, or relative lack thereof, of the treatment.

Furthermore, it is aptly noted that a different set of assays is used to determine whether an agent has the ability to inhibit metastasis, as opposed to the growth of tumor cells; and since an agent that inhibits the growth of a tumor cell may not as effectively inhibit its metastasis, and vice versa, such independent evaluations of the agent's abilities to achieve these different effects would be prudent. Accordingly, even preliminary, or preclinical evaluation of the effectiveness of different polypeptides comprising inhibitory amino-terminal fragments of ATF2 to inhibit growth or metastasis will differ substantially; such differences underscore additional reasons why there is art-recognized divergence in the subject matter of the newly added claims, relative to that of claims 1, 4, 8-12, and 35-43.

While claims 23-29 are broadly directed to a method for treating a tumor, the merit of those claims has only been considered thus far to the extent that the method reads on the process of claims 1, 4, 8-12, and 35-43, as opposed to the process of newly added claims 45-47.

Because these inventions of claims 45-47 and the inventions of claims 1, 4, 8-12, 23-29, and 35-43 are distinct for the reasons given above, the search required for one is not the same, nor is it coextensive with that required for the other. Moreover, because of the differences in objective, for example, the inventions have acquired a separate status in the art as shown by their recognized divergent subject matter. As such, searching the subject matter encompassed by claim 45-47 would require a new search, and the need to perform an additional search would constitute a serious burden. Therefore, restriction for examination purposes as indicated is proper.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for

prosecution on the merits. Accordingly, claims 45-47 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Grounds of Objection and Rejection Withdrawn

6. Applicant's amendment and/or arguments filed December 9, 2005, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed September 9, 2005.

For clarity, the rejection of claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43 under 35 U.S.C. §§ 102 and/or 103 have been withdrawn because claims 1 and 13 recite the limitation "wild-type". It is understood that the use of the term "wild-type" to describe a polypeptide, such as ATF2, connotes the polypeptide has a naturally occurring amino acid sequence, which differentiates the "inhibitory N-terminal fragment" to which the claims are directed from the "inhibitory N-terminal fragment" taught by the prior art, since the latter comprises a non-naturally occurring amino acid sequence, which was engineered in the laboratory by site-directed mutagenesis. Then, with further particular regard to claim 4, the prior art does not teach or fairly suggest an "inhibitory N-terminal fragment of ATF2", which *consists of* the region of ATF2 spanning from about amino acid 50 to about amino acid 75, and although claim 4 is indefinite for the reason set forth below, it has been interpreted as if it were drawn to such limited subject matter, as further explained below.

Priority

7. Applicant's claim under 35 USC § 119(e) for benefit of the earlier filing date of U.S. Provisional Application No. 60/269,257, filed February 16, 2001, and U.S. Provisional Application No. 60/269,118, filed February 15, 2001, is acknowledged.

However, claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description.

To receive benefit of the earlier filing date under 35 USC § 119(e), the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely February 14, 2002.

Response to Arguments

8. At page 26 of the amendment filed December 9, 2005, it is noted that Applicant has argued that the mutant ATF2 taught by van Dam is not a "dominant negative". In response, it is aptly noted that Bhoumik et al. teaches that phosphorylation-deficient full-length ATF2 molecules have effects similar to those of the amino-terminal truncated form, which serves as a dominant-negative; see, e.g., page 340, column 2. Accordingly, it appears that contrary to Applicant's argument, the phosphorylation-deficient mutant ATF2 molecule taught by van Dam is described as having the equivalent effect of, if not actually properly termed a "dominant negative".

Otherwise, Applicant's arguments with respect to grounds of rejection set forth in the preceding Office, which have not been maintained herein, have been considered but are moot in view of the new ground of rejection set forth below.

New Grounds of Objection

9. Claims 4 and 12 are objected to because the claims recite, "the inhibitory N-terminal fragment of ATF2", as opposed to "the inhibitory N-terminal fragment of wild-

type ATF2" (emphasis added), which arguably might not find proper antecedent basis in the preceding claim. Appropriate correction or rebuttal is required.

10. Claims 13 and 29 are objected to because the claims recite, "the inhibitory N-terminal fragment of ATF2", as opposed to "the inhibitory N-terminal fragment of wild-type ATF2" (emphasis added), which arguably might not find proper antecedent basis in the claim itself or in the preceding claims, respectively. Appropriate correction or rebuttal is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43 are indefinite because claims 1 and 13 recite "wild-type ATF2" as the sole means of identifying the polypeptide to which the claims refer. The use of such "laboratory" designations only to identify a particular polypeptide renders the claims indefinite because different laboratories may use the same laboratory designations to define distinct polypeptides.

At page 21 of the amendment filed December 9, 2005, Applicant has asserted that the specification "makes it clear that the sequence used for the experiments was amino acids 50-100 of the normal, human, ATF2 sequence, which was known in the art since 1989 (see attached printout from GenBank; accession number NP_008171)" (paragraph 3). However, contrary to Applicant's assertion, the specification does not make this clear, since nowhere in the specification does it appear this particular sequence mentioned.

Because of polymorphism (i.e., natural variation), there is normal (i.e., "wild-type") variation in the sequences of structurally distinct alleles encoding isoforms of "ATF2"; this concept has recently been reviewed[2]. Because of the variation in the polynucleotide sequences of these distinct alleles, the polypeptides encoded by these alleles may vary structurally and/or functionally. As a further source of ambiguity, because the gene encoding "ATF2" is alternatively spliced[3], there are structurally and functionally distinct isoforms of "ATF2", which occur naturally. Accordingly, it is not evident to which particular polypeptide designated "wild-type ATF2" the claims are directed.

In fact, because the specification does not appear to describe the amino acid sequence of the polypeptide designated "ATF2", it was presumed earlier during the course of prosecution that a search of relevant sequence databases using as a query the amino acid sequence set forth as GenBank™ Accession No. AAH26175 would suffice. The reason that this sequence was chosen is that it is annotated as the amino acid sequence of human ATF2 encoded by the complete coding sequence of an isolated messenger RNA (mRNA) having the GenBank™ Accession No. BC026175. However, Applicant has asserted that the amino acid sequence of the polypeptide to which the claims refer is not *this* sequence, but a different sequence set forth as GenBank; accession number NP_008171. Thus, the use of laboratory nomenclature alone cannot suffice, at least in this instance, to clearly and particularly point out the subject matter to which the claims are directed.

Accordingly, the claim does not delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph.

The above-mentioned discrepancy illustrates the need to identify the polypeptide to which the claims refer using an identifier that unambiguously identifies that polypeptide. The amino acid sequence of a polypeptide is a unique identifier that

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[2] See Crawford et al. (*Annu. Rev. Genomics Hum. Genet.* 2005; **6**: 287-312); entire document.

unambiguously defines a given polypeptide. Accordingly, this issue might be remedied by amending claims 1 and 13 to include the amino acid sequence of the polypeptide by reference to a specific sequence identification number of an amino acid sequence set forth in the Sequence Listing.

However, as Applicant has noted at page 21, paragraph 3, of the amendment filed December 9, 2005, the specification dose not depict the sequence of the polypeptide to which the claims are directed, and moreover the specification does not contain a sequence listing. Therefore, the only possible remedial action that may be suggested at present is to incorporate by reference into the specification the amino acid sequence of the polypeptide to which the claims refer, with the *proviso* that there is a nexus between a cited reference teaching this amino acid sequence and the amino acid sequence of the polypeptide to which the claims refer.

(b) Claims 1, 4, 8-12,and 35-43 are indefinite because claim 1 recites a term in parentheses (i.e., "Peptide II"). It cannot be ascertained whether the parenthetically enclosed term is meant to delineate, or limit the subject matter of the claims, or simply meant to be exemplary, parenthetical, or redefining. Accordingly, the claim does not delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph.

(c) Claims 4 is indefinite because the claim recites, "wherein the inhibitory N-terminal fragment of ATF2 consists of amino acid residues from about residue 50 of ATF2 to about 75 of ATF2". Since claim 4 depends from claim 1, which recites a limitation requiring the inhibitory N-terminal fragment of ATF2 to comprise amino acid residues from about residue 50 to about residue 100", the recitation of the limitation in claim 4 renders that claim indefinite. An amino-terminal fragment of ATF2 cannot consist of the region of ATF2 that spans from about residue 50 to about residue 75 and also comprise an additional region of ATF2 (i.e., the region spanning from about residue

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[3] See, e.g., Bailey et al. (*J. Mol. Endocrinol.* 2005 Feb; **34** (1): 19-35); see entire document.

76 to about residue 100). Accordingly, the claim does not delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph.

13. Claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

Claims 1, 4, 8-13, 15, 20, 21, 23-29, and 35-43 recite "wild-type" ATF2.

At page 26 of the amendment filed December 9, 2005, Applicant has asserted that support for the amendment of claims 1 and 13 is found, for example, at pages 40, 41, and 51 of the specification.

Contrary to Applicant's assertion, however, it does not appear that the specification, including the claims, as originally filed, provides written support of the term "wild-type" as it is used in the claims to describe an "ATF2" polypeptide.

Although the term "wild-type" is used in the specification to describe a "GFP" polypeptide[4] and "fibroblasts"[5], it is not used to describe any "ATF2" polypeptide.

The sentence at page 51 (lines 12 and 13) to which Applicant has referred describes "Peptide II" as harboring "amino acid residues 50-100 of the ATF2 cDNA, which contains the phosphorylation sites for the stress kinases p38 and JNK". Though the sentence is somewhat nonsensical, since a cDNA does not comprise amino acids, it does not provide written support for the use of the term "wild-type" in its given context in the claims (i.e., as a descriptor of "ATF2").

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[4] See, e.g., page 36, line 20, of the specification, as originally filed.
[5] See, e.g., page 60, lines 27 and 28, of the specification, as originally filed.

The sentence at page 41 (lines 5-8) to which Applicant has referred describes the importance of amino acids at positions 69 and 71 of the amino acid sequence of ATF2, as described by Gupta et al. This disclosure does not provide written support for the use of the term "wild-type" in its given context in the claims (i.e., as a descriptor of "ATF2").

The sentence at page 40 (lies 4-7) to which Applicant has referred describes preparation of oligonucleotides coding for peptides consisting of fragments of ATF2. This disclosure does not provide written support for the use of the term "wild-type" in its given context in the claims (i.e., as a descriptor of "ATF2").

Furthermore, it is again noted that at page 21 of the amendment filed December 9, 2005, Applicant has asserted that the specification "makes it clear that the sequence used for the experiments was amino acids 50-100 of the normal, human, ATF2 sequence, which was known in the art since 1989 (see attached printout from GenBank; accession number NP_008171)" (paragraph 3). However, contrary to Applicant's assertion, the specification does not make this clear, since nowhere in the specification does it appear this particular sequence mentioned, and moreover the specification does not provide a nexus between "wild-type" ATF2, as recited in the claims, and the amino acid sequence set forth as GenBank™ Accession No. NP_008171.

For these reasons, it appears the amendment of claims 1 and 13 to recite the term "wild-type" as a descriptor of "ATF2" has introduced new matter in violation of the written description requirement set forth under 37 U.S.C. § 112, first paragraph.

This issue might be remedied if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 13 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Livingstone et al. (*EMBO J.* 1995; **14** (8): 1785-1797).

Livingstone et al. teaches a composition comprising a polypeptide comprising an amino-terminal fragment of ATF2, which consists essentially of (i.e., comprises) amino acid residues from about residue 50 to about residue 100, and a pharmaceutically acceptable carrier or excipient; see entire document (e.g., page 1786, Figure 1; and page 1796, column 1).

16. Claims 1, 8-13, 20, and 35-43 are rejected under 35 U.S.C. 102(a) as being anticipated by Bhoumik et al. (*Clin. Cancer Res.* 2001 Feb; **7** (2): 331--342) (of record), as evidenced by Bhoumik et al. (*Proc. Natl. Acad. Sci USA.* 2004 Mar 23; **101** (12): 4222-4227).

Bhoumik et al. (2001) teaches an amino-terminal fragment of ATF2, which consists of amino acids 50-100 of the full-length protein; see entire document (e.g., the abstract). Bhoumik et al. teaches this fragment of ATF2 inhibited the growth of melanoma in mice (page 341, column 1). Bhoumik et al. (2001) teaches contacting tumor cells (e.g., late-stage melanoma cells; breast cancer cells) *in vitro* with this fragment of ATF2 increased their apoptosis, sensitizing the cells to the effects of chemotherapeutic agents, such as UCN-01 or the p38 inhibitor SB203580, and irradiation with ultraviolet light (e.g., the abstract; page 332, column 1; page 336, Figure 5; pages 337 and 338, Figure 6; page 341, column 1). Moreover, Bhoumik et al. (2001) teaches contacting tumor cells with this fragment of ATF2 and further treating the cells with NCS; see, e.g., page 335, Figure 3. Bhoumik et al. (2001) teaches the mechanism by which this fragment of ATF2 increases sensitivity of tumor cells to irradiation and chemotherapeutic agents likely involves competition with endogenous forms of ATF2

(page 340, column 2). Consistently, Bhoumik et al. (2001) teaches transcriptional activities mediated by AP1 target sequences, which are regulated by c-Jun-ATF2 heterodimers, are lower in melanoma cells contacted with this fragment of ATF2 (e.g., page 340, column 2).

Bhoumik et al. (2001) does not expressly teach that the process of contacting tumor cells with the inhibitory amino-terminal fragment of ATF2 causes a relative increase in the activity of JNK in those cells, as compared to the activity of JNK in cells not contacted with peptide. Nevertheless, as evidenced by Bhoumik et al. (2004), the process results in the sequestration of endogenous ATF2 to the cytoplasm, thus inhibiting its transcriptional activity, and concomitantly increases in the activity of JNK; see entire document (e.g., the abstract; page 4227, column 1).

For clarity: Although claim 4 is indefinite for the reason explained in the above rejection under 35 U.S.C. § 112, second paragraph, claim 4 has not been included in this rejection because it has been interpreted as *if* it were drawn to the method of claim 1 wherein the inhibitory N-terminal fragment of wild-type ATF2 consists of amino acids from about 50 to about 75 of ATF2.

Claim Rejections - 35 USC § 103

17. Claims 15 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livingstone et al. (*EMBO J.* 1995; **14** (8): 1785-1797) in view of Nilsson et al. (*Nucleic Acid Res.* 1985; **13** (4): 1151--1162).

Livingstone et al. teaches that which is set forth in the above rejection of claims 13 and 20 under 35 U.S.C. 102(b).

However, Livingstone et al. does not teach or expressly suggest a fusion polypeptide comprising an amino-terminal fragment of ATF2, which consists essentially of (i.e., comprises) amino acid residues from about residue 50 to about residue 100, and further comprising a translocation peptide sequence.

Nonetheless, Nilsson et al. teaches the production of recombinant polypeptides using a staphylococcal protein A expression vector system; see entire document (e.g.,

the abstract). Nilsson et al. teaches the recombinant polypeptides produced using this system are fusion proteins comprising a foreign gene product and staphylococcal protein A (see, e.g., the abstract; pages 1159-1161, "Discussion"). Nilsson et al. teaches staphylococcal protein A fusion proteins are translocated through the cytoplasmic membrane with the aid of a signal sequence (see, e.g., paragraph bridging pages 1151 and 1152). Nilsson et al. teaches staphylococcal protein A fusion proteins are efficiently purified by IgG affinity chromatography (see, e.g., page 1151, "Introduction"). Nilsson et al. teaches, after affinity purification, compositions comprising the fusion protein are treated to remove the staphylococcal protein A "tail" and release the foreign gene product (see, e.g., page 1152, "Introduction"; page 1154, Figure 1).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to produce fusion polypeptides comprising amino-terminal fragments of ATF2, which comprise the amino acid residues from about residue 50 to about residue 100 of ATF2, and further comprising a translocation peptide using the staphylococcal protein A expression vector system described by Nilsson et al., because Livingstone et al. teaches making and using such fragments of ATF2 and Nilsson et al. teaches the expression system is used advantageously since, for example, the resulting product is a fusion protein comprising the protein of interest and staphylococcal protein A, which is efficiently purified by IgG affinity chromatography. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so to produce purified fusion polypeptides comprising the amino-terminal fragments of ATF2 described by Livingstone et al.

18. Claims 23-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bhoumik et al. (*Clin. Cancer Res.* 2001 Feb; **7** (2): 331--342) (of record), as evidenced by Bhoumik et al. (*Cancer Res.* 2004 Nov 15; **64**: 8222-8230).

Bhoumik et al. (2001) teaches that which is set forth in the above rejection of claims 1, 8-13, 20, and 35-43 under 35 U.S.C. 102(a).

However, Bhoumik et al. (2001) does not expressly teach a process for treating a tumor in a subject comprising administering a therapeutically effective amount of a pharmaceutical composition comprising the amino-terminal fragment of ATF2.

Nonetheless, as noted in the above rejection of claims 1, 8-13, 20, and 35-43 under 35 U.S.C. 102(a), Bhoumik et al. (2001) teaches contacting melanoma cells in nude mice with the fragment of ATF2 inhibited the growth of those cells (page 341, column 1). Given this disclosure, in particular, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to treat a tumor (i.e., a melanoma) in a subject by administering to the subject a pharmaceutical composition comprising an amount of fragment of ATF2 to achieve the therapeutic effect of inhibiting the growth of that tumor. Moreover, because Bhoumik et al. (2001) teaches the fragment of ATF2 inhibited the growth of melanoma cells in mice, which were contacted with the fragment (page 341, column 1), one ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of successfully practicing this process to achieve such a therapeutic effect. In addition, because Bhoumik et al. (2001) teaches contacting melanoma cells and breast cancer cells *in vitro* with this same fragment of ATF2 increased their apoptosis and increased their sensitivities to the anti-proliferative effects of chemotherapeutic agents, such as UCN-01 or SB203580, and irradiation with ultraviolet light (e.g., the abstract; page 336, Figure 5; pages 337 and 338, Figure 6; page 341, column 1), it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to treat a tumor (i.e., a melanoma) in a subject by administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of the fragment of ATF2 in combination with treatments using chemotherapeutic agents, including, for example, UCN-01, NCS or the p38 inhibitor SM203580, or treatments using ultraviolet radiation. Accordingly, one ordinarily skilled in the art at the time the invention was made would have been motivated to do so to treat a tumor in a subject.

As evidenced by Bhoumik et al. (2004), the process of administering a polypeptide comprising an amino-terminal fragment of ATF2 consisting of amino acids

51-100 of ATF2 to mice is effective to treat tumors in those mice; see entire document (e.g., the abstract).

19. Claims 15, 21, and 23-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bhoumik et al. (*Clin. Cancer Res.* 2001 Feb; **7** (2): 331—342) (of record) in view of Mi et al. (*Mol. Ther.* 2000 Oct; **2** (4): 339-347).

Here, claims 23-29 are rejected to the extent that the claims are directed to the pharmaceutical composition of claim 21.

Bhoumik et al. teaches that which is set forth in the above rejection of claims 1, 8-13, 20, and 35-43 under 35 U.S.C. 102(a) and the above rejection of claims 23-29 under 35 U.S.C. 103(a).

However, Bhoumik et al. does not expressly teach a process for treating a tumor in a subject comprising administering a therapeutically effective amount of a pharmaceutical composition comprising a fusion protein comprising the amino-terminal fragment of ATF2 and further comprising a translocation peptide.

Even so, Mi et al. teaches cationic peptides that facilitate efficient transduction (i.e., translocation) of proteins *in vivo*; see entire document (e.g., the abstract). Moreover, Mi et al. teaches these peptides facilitated rapid and efficient delivery of proteins into solid tumors and accordingly Mi et al. concludes these peptides are therapeutically useful; see, e.g., the abstract.

Therefore, because Bhoumik et al. teaches contacting melanoma cells in nude mice with the fragment of ATF2 inhibited the growth of those cells (page 341, column 1), it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to treat a tumor (i.e., a melanoma) in a subject by administering to the subject a pharmaceutical composition comprising an amount of a fusion protein comprising the amino-terminal fragment of ATF2 and further comprising a translocation peptide to achieve the therapeutic effect of inhibiting the growth of that tumor, since Mi et al. teaches translocation peptides facilitate efficient protein transduction *in vivo*. Moreover, because Bhoumik et al. teaches the fragment of ATF2 inhibited the growth of melanoma cells in mice, which were contacted with the fragment (page 341, column 1),

and because Mi et al. teaches translocation peptides facilitate efficient protein transduction *in vivo,* one ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of successfully practicing this process to achieve such a therapeutic effect. In addition, because Bhoumik et al. teaches contacting melanoma cells and breast cancer cells *in vitro* with this same fragment of ATF2 increased their apoptosis and increased their sensitivities to the anti-proliferative effects of chemotherapeutic agents, such as UCN-01 or SB203580, and irradiation with ultraviolet light (e.g., the abstract; page 336, Figure 5; pages 337 and 338, Figure 6; page 341, column 1), it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to treat a tumor (i.e., a melanoma) in a subject by administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of the fusion protein comprising the amino-terminal fragment of ATF2 and further comprising a translocation peptide in combination with treatments using chemotherapeutic agents, including, for example, UCN-01, NCS or the p38 inhibitor SM203580, or treatments using ultraviolet radiation. Accordingly, one ordinarily skilled in the art at the time the invention was made would have been motivated to do so to treat a tumor in a subject.

Conclusion

20. No claim is allowed.

21. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Jobling et al. (*Plasmid*. 1997; **38**: 158-173) teaches a versatile cloning vector for efficient delivery of recombinant fusion proteins comprising a translocation peptide (i.e., the LTIIb B leader) to the periplasm of *E. coli*. Abdel-Hafiz et al. (*Mol. Endocrinol.* 1992 Dec; **6** (12): 2079-2089) teaches an amino-terminal fragment of ATF2. Duyndam et al. (*Oncogene*. 1999; **18**: 2311-2321) teaches an amino-terminal fragment of ATF2. Ronai et al. (*Oncogene*. 1998; **16**: 523-531) (of record) teaches ATF2 confers radiation resistance to melanoma cells.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

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